

Clinical Study Protocol

A Phase II Clinical Trial of the Efficacy and Safety of Short-term (3 days) Enoxaparin for the Prevention of Venous Thromboembolism after Gastric Cancer Surgery

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Although intermittent pneumatic compression (IPC) has become common as perioperative prophylaxis for venous thromboembolism (VTE) consisting of pulmonary thromboembolism (PE) and deep vein thrombosis (DVT), the prophylactic effect against VTE, especially lethal PE, is not yet satisfactory. Therefore, pharmacologic prophylaxis, such as with enoxaparin, is desirable. While the efficacy and safety of enoxaparin have been proven in several clinical trials, concern about bleeding with long-term (at least 7 days) use have potentially decreased its widespread adoption. We have launched a phase II study to evaluate the efficacy and safety of short-term (3 days) enoxaparin, in which a total of 70 gastric cancer patients undergoing gastrectomy will be recruited, and the primary endpoint is the incidence of DVT. This study could contribute to making pharmacologic prophylaxis for VTE more common.

Key words: venous thromboembolism, enoxaparin, short-term use, gastric cancer, surgery

Venous thromboembolism (VTE) consists of pulmonary thromboembolism (PE) and deep vein thrombosis (DVT). PE and DVT are divided into symptomatic and asymptomatic depending on the presence or absence of symptom. VTE, especially PE, is one of the critical postoperative complications that can cause sudden death; therefore, preventing VTE in the perioperative period is recognized as indispensable. Against this backdrop, guidelines for VTE prevention were established in 2004 in Japan, in which the risk for VTE is classified into 4 categories, and a prevention strategy is proposed for each category [1]. Most abdominal surgeries for cancer patients are included

in the high-risk group, for which either mechanical prophylaxis with intermittent pneumatic compression (IPC) or pharmacologic prophylaxis is recommended in this guideline. Although prophylaxis with IPC has spread steadily across the country and reduced the incidence of perioperative VTE to some degree, around 20% (17.6%-23.7%) of patients who underwent abdominal surgery were still diagnosed with DVT, from which lethal PE could result, even with mechanical prophylaxis by IPC in prospective clinical studies [2-4]. In addition, the mortality rate associated with perioperative PE has not decreased much since publication of the guideline [5]. Therefore, pharmacologic prophylaxis has been increasingly considered neces-

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sary for patients who undergo major abdominal surgery unless they have active bleeding or a high bleeding risk.

Detailed information about pharmacologic prophylaxis for VTE in cancer patients is described in the guideline from the American Society of Clinical Oncology (ASCO), in which pharmacologic prophylaxis with unfractionated heparin (UFH) or low molecular weight heparin (LMWH) such as enoxaparin for at least 7–10 days is recommended [6], while no detailed information is provided in the Japanese guideline. In the ENOXACAN study, which was the first randomized clinical trial comparing the prophylactic use of enoxaparin with UFH in cancer patients who underwent abdominal or pelvic surgery, the frequency of VTE was lower in the enoxaparin group (14.7%) than in the UFH group (18.2%), while there were no differences in bleeding events or other complications [7]. In a meta-analysis comparing LMWH and UFH, LMWH seemed to be as effective and safe as UHF [8]. With the growing need for pharmacologic prophylaxis for VTE in Japan, a multicenter, randomized, clinical trial conducted in patients undergoing curative abdominal or pelvic cancer surgery showed that 14-day use of enoxaparin reduced the incidence of VTE to only 1.2% compared to 19.4% for IPC [4].

Despite these impressive results of LMWHs such as enoxaparin, prophylactic use of LMWH still remains uncommon in abdominal surgery in Japan due to concerns about postoperative bleeding. In addition, if enoxaparin is used for at least 7 days after surgery

as recommended in the ASCO guideline, an abdominal drain or an epidural catheter for pain control needs to be removed during enoxaparin use, which could increase the risk of bleeding-related complications caused by removal of a drain or an epidural catheter. If short-term (3 days) use of enoxaparin is as effective and safe as regular use, this method allows us to remove an abdominal drain and an epidural catheter after the completion of enoxaparin use, which can contribute to reducing the risk for bleeding-related complications and making our postoperative management easier compared to regular use of enoxaparin.

Thus, we have launched a single-arm, prospective, non-randomized, non-comparative, open label, single-center phase II clinical study to evaluate the efficacy and safety of short-term (3 days) use of enoxaparin after surgery to prevent VTE in gastric cancer patients who undergo curative gastrectomy. Fig. 1 shows an overview of the study design. This study is being conducted in compliance with the principles of the Declaration of Helsinki, and this protocol has been approved by the institutional review board of Okayama University (No. 1512-002). The UMIN registration number of this study is 000020235.

Endpoints

The primary endpoint is the incidence of DVT, which is basically examined with ultrasonography of the lower limbs between postoperative day (POD) 8 and POD 14 and diagnosed by a cardiovascular physi-

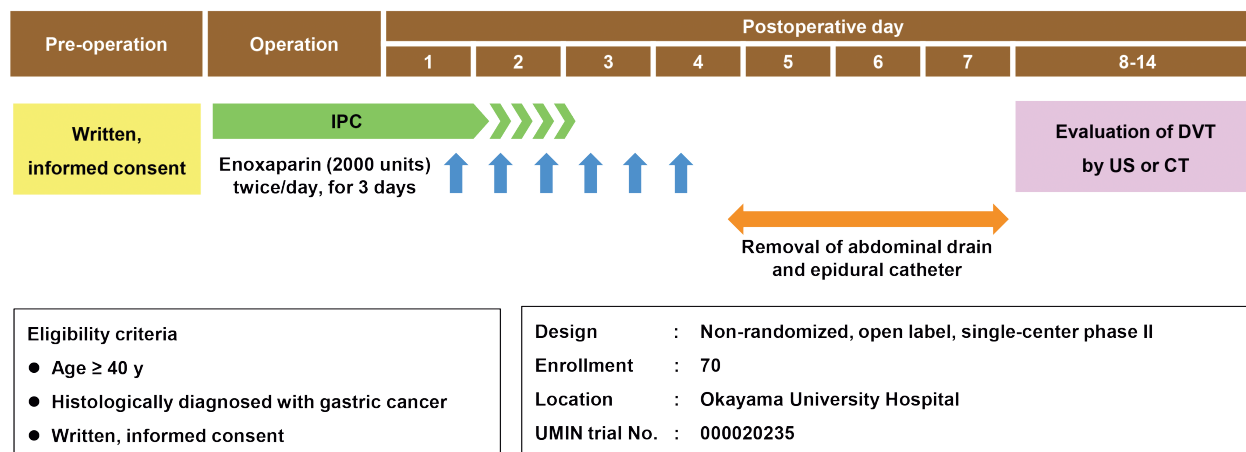


Fig. 1 Overview of the study design IPC, intermittent pneumatic compression.

cian not involved in this study. If systemic examination is judged necessary for the diagnosis of VTE, especially PE, contrast-enhanced computed tomography is alternatively permitted as a diagnostic modality for DVT, which is diagnosed in this case by a radiologist not involved in this study.

The secondary endpoint is the incidence of bleeding-related adverse events, which are classified into 2 groups, major and minor bleeding events, according to the criteria reported previously [4]. Safety is also evaluated based on the incidence of adverse events not related to bleeding.

All patients will be followed-up until a regular checkup at approximately 1 month after surgery. All adverse events are recorded according to the Clavien-Dindo classification (ver. 2.0) [9]. Information about each patient's background, surgery, pathology, and pre- and post-operative laboratory data is also to be obtained from the medical record.

Eligibility Criteria

All patients who meet the eligibility criteria based on the inclusion and exclusion criteria will be invited for screening. The main inclusion and exclusion criteria are listed in Table 1. Written, informed consent must be obtained from the patient by an investigator before intervention. Patients who do not participate in this study have VTE prophylaxis based on the guideline.

Treatment Methods

After written, informed consent is obtained preop-

eratively, prophylaxis for VTE is performed with 2 methods of IPC and enoxaparin in the perioperative period. Use of IPC starts during operation and continues until patients are able to walk adequately after surgery. Enoxaparin (20 mg, 2,000 units) is subcutaneously injected twice a day for 3 days, starting 36 h after surgery (in the evening of POD 1) and continues until the morning of POD 4. Delay of initiation of enoxaparin due to concern over bleeding-related complications is permitted at a physician's discretion; however, enoxaparin is injected 6 times in total until POD 7 in principle. Enoxaparin is used once a day for 3 days for patients with creatinine clearance of 30–50 ml/min. An abdominal drain and an epidural catheter are removed more than 10–12 h after the final injection of enoxaparin.

Statistical Consideration

The estimated incidence of VTE with mechanical prophylaxis with IPC is approximately 18% based on the incidence in two phase III clinical studies conducted in Japanese cancer patients undergoing abdominal surgery [3,4]. From the result in total hip or knee replacement patients showing a 50% reduction in the VTE risk of Japanese patients who were treated by at least 7 days use of enoxaparin [10], the estimated risk of VTE would be 9% with at least 7 days use of enoxaparin. When 3 days of enoxaparin is assumed to have a similar prophylactic effect as at least 7 days, the estimated risk of VTE with 3 days of enoxaparin would also be 9%.

At the first stage, 62 evaluable patients are required based on an estimated incidence of 9% and an

Table 1 Patient eligibility

Inclusion criteria	
	Aged 40 years or older
	Histologically diagnosed with gastric cancer
	Written, informed consent
Exclusion criteria	
	History of venous thromboembolism
	History of allergic reaction to heparin or heparinoid (including LMWH)
	Active bleeding (except for bleeding from gastric cancer planned to be resected)
	Acute bacterial endocarditis
	Serious renal disorder (Ccr < 30 ml/min)
	History of heparin-induced thrombocytopenia
	Otherwise judged by the investigator as unsuitable for enrollment

LMWH, low molecular weight heparin; Ccr, creatinine clearance.

upper limit of incidence of 20% with alpha of 0.05 and beta of 0.2 according to Simon's two-stage design [11]. If 8 or fewer incidences are observed among these first stage patients, an additional 4 patients will be entered. At the time of final analysis, less than 8 incidences among 66 patients will indicate that enoxaparin for 3 days merits further investigation. A total of 70 patients is planned to be recruited in this study taking into account some unevaluable patients. An interim analysis is planned after the first 31 patients, half of the patients in the first stage, for reconsideration of sample size.

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